Xanthones. Part IV. A New Synthesis of Hydroxyxanthones and Hydroxybenzophenones.*

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Hydroxy-xanthones and -benzophenones are conveniently obtained from hydroxybenzoic acids and phenols in presence of zinc chloride and phosphorus oxychloride.

DISTILLATION of a mixture of a phenol, a phenolic acid, and acetic anhydride is the earliest and simplest method for the synthesis of hydroxyxanthones (Michael, *Amer. Chem. J.*, 1883, **5**, 81; Kostanecki and his co-workers, *Ber.*, 1891, **24**, 1896, 3981, etc.; Lund, Robertson, and Whalley, *J.*, 1953, 2438), but yields are often poor, experimental conditions are rather drastic, and there is a possibility of decarboxylation, autocondensation, and other side reactions (Lespegnol, Bertrand, and Dupas, *Bull. Soc. chim. France*, 1939, **6**, 1925; Lund *et al.*, *loc. cit.*). There are numerous other routes, but none is of general application and some require uncommon starting materials or involve a number of steps.

In continuation of the work on naturally occurring xanthones (*J. Indian Chem. Soc.*, 1953, **30**, 457, 463; *J. Sci. Ind. Res., India*, 1954, **13**, *B*, 175; 1955, **14**, *B*, 153) the known methods for the synthesis of 1 : 3 : 7 : 8-tetrahydroxyxanthone or its tetramethyl ether

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were found unsuitable. Condensation under mild conditions of a phenolcarboxylic acid with a reactive phenol in presence of condensing agents such as anhydrous aluminium chloride, phosphorus oxychloride, phosphoric oxide, or sulphuric acid was not promising; but a mixture of phosphorus oxychloride and fused zinc chloride, which had previously been found effective for the preparation of 2 : 4-dihydroxybenzophenone (Shah and Mehta, *J. Indian Chem. Soc.*, 1936, **13**, 368) gave highly satisfactory results, thus providing a new and convenient method for the synthesis of hydroxyxanthones (*Chem. and Ind.*, 1955, 62). In this method condensation of an *o*-hydroxybenzoic acid and a reactive phenol at about 60—80° for 1—2 hours, or in some cases even at room temperature, yields a hydroxyxanthone or a hydroxybenzophenone. The latter are best cyclised to xanthones by heating them alone at about 200—220° (Meyer and Conzetti, *Ber.*, 1897, **30**, 969) or with water in a sealed tube or in an autoclave at about 180—220° (Dutta and Watson, *J. Soc. Chem. Ind.*, 1911, **30**, 196), the latter method giving almost quantitative yields. It is interesting that oximation of 2 : 2′ : 4 : 4′-tetrahydroxybenzophenone gave the oxime of 3 : 6-dihydroxyxanthone, cyclisation having taken place simultaneously; however the oxime could not be hydrolysed to 3 : 6-dihydroxyxanthone.

The use of zinc chloride or phosphorus oxychloride alone is ineffective or much less efficient. Nenki's reaction, using fused zinc chloride alone, has been previously used for the preparation of some hydroxy-benzophenones and -xanthones, but the experimental conditions required are drastic and so the method is of limited use (Dutta and Watson, *J.*, 1912, **101**, 1238; Kostanecki, *Ber.*, 1894, **27**, 1989; Seshadri and Pankajmani, *J. Sci. Ind. Res., India*, 1954, **13**, *B*, 396).

A number of mono-, di-, and tri-hydroxybenzoic acids have been condensed with reactive phenols in typical syntheses by this method and ten xanthones and four benzophenones (some of them new) have been obtained. The following points are of interest: (1) Gentisic acid failed to condense, but its 5-monomethyl ether, did condense. (2) The method can be used when one or both the components is methylated. (3) Hydroxybenzoic acids condense in the β-position of the resorcinol nucleus as normally expected, whereas in Kostanecki's method condensations take place both in the β- and the γ-position, giving a mixture of 3 : 6- and 3 : 8-dihydroxyxanthones (Graebe, *Annalen*, 1889, **254**, 302; Bistrzycki and Kostanecki, *Ber.*, 1885, **18**, 1987). Orcinol condenses in the γ-position (cf. Shah and Saraiya, *Proc. Indian Acad. Sci.*, 1950, **31**, *A*, 213). (4) Xanthones are obtained directly when the acid component is a 2 : 6-dihydroxybenzoic acid, such as γ-resorcylic acid or phloroglucinolcarboxylic acid, or when the phenol is phloroglucinol or orcinol; *i.e.*, when the intermediate is a 2 : 6-dihydroxybenzophenone, it instantaneously cyclises to xanthone and cannot be isolated. This and the cyclisation during oximation may have a stereochemical cause.

EXPERIMENTAL

General Procedure.—A mixture of an *o*-hydroxybenzoic acid, a phenol, fused zinc chloride, and phosphorus oxychloride was heated on a water-bath for 1½—2 hr., then cooled and poured into ice-water. The product was filtered off, washed with sodium hydrogen carbonate solution, and water, dried, and crystallised from suitable solvent. Acetates were prepared by acetic anhydride-pyridine, and methyl ethers by methyl sulphate, potassium carbonate, and acetone.

1 : 3-*Dihydroxyxanthone.*—Salicylic acid (1 g.), phloroglucinol (1·4 g.), freshly fused zinc chloride (3 g.), and phosphorus oxychloride (7 c.c.) were heated at 60—70° for 2 hr. The product was sublimed at 2 mm. and crystallised from dilute alcohol in needles, m. p. 256—258° (0·8 g.) (Robinson and Nishikawa, *J.*, 1922, **121**, 839, give m. p. 256—258°). The dimethyl ether crystallised as needles, m. p. 169—170°, from alcohol (Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 710, give m. p. 167—169°), and the diacetate, crystallised from alcohol, had m. p. 149° (*idem, ibid.*, give m. p. 145°) (Found: C, 65·3; H, 3·8. Calc. for $C_{17}H_{12}O_6$: C, 65·4; H, 3·9%).

2 : 2′ : 3 : 4-*Tetrahydroxybenzophenone.*—Salicylic acid (1 g.), pyrogallol (1·4 g.), zinc chloride (3 g.), and phosphorus oxychloride (7 c.c.) at 60—70° (2 hr.) gave the benzophenone, plates (from water), m. p. 103—104° which rose to 149° after drying at 100° in a vacuum (yield, 0·9 g.). This gave a blackish-green ferric reaction (Graebe and Eichengrün, *Annalen*, 1892,

269, 307, gave m. p. 102° with 1H_2O) (Found : C, 63·4; H, 4·2. Calc. for $C_{13}H_{10}O_5$: C, 63·4; H, 4·1%). The *tetra-acetate*, crystallised from alcohol, had m. p. 117—118° (Found : C, 61·0; H, 4·6. $C_{21}H_{18}O_9$ requires C, 60·9; H, 4·3%).

3 : 4-*Dihydroxyxanthone*.—The foregoing benzophenone (0·5 g.) and water (20 c.c.) were heated under pressure at 180—200° for 5 hr. The solid xanthone produced crystallised from dilute alcohol as yellow plates, m. p. 240—241° (Graebe and Ullmann, *Ber.*, 1896, **29**, 824, give m. p. 240—241°). The dimethyl ether crystallised from alcohol in needles, m. p. 157° (Ullmann and Dinzler, *Ber.*, 1906, **39**, 433, give m. p. 156—158°). The diacetate (from alcohol) had m. p. 163—164° (Rao and Seshadri, *loc. cit.*, give m. p. 161—162°).

2 : 2′ : 4 : 4′-*Tetrahydroxybenzophenone*.—β-Resorcylic acid (5 g.), resorcinol (5 g.), freshly fused zinc chloride (20 g.), and phosphorus oxychoride (25 c.c.) were heated at 80—90° for 45 min. or kept for 48 hr. at room temperature. The benzophenone crystallised from boiling water in needles, m. p. 196—198° (6 g.) (Found : C, 63·1; H, 4·2. Calc. for $C_{13}H_{10}O_5$: C, 63·4; H, 4·1%). Shoesmith and Haldane (*J.*, 1924, **125**, 113) give m. p. 196—198°. The tetramethyl ether, crystallised from dilute alcohol, had m. p. 126—128° (Staudinger, Schlenker, and Goldstein, *Helv. Chim. Acta*, 1921, **4**, 341, give m. p. 129—130°), and the *tetra-acetate* (from alcohol), needles, had m. p. 146—147° (Found : C, 60·7; H, 4·25. $C_{21}H_{18}O_9$ requires C, 60·9; H, 4·4%).

3 : 6-*Dihydroxyxanthone Oxime from* 2 : 2′ : 4 : 4′-*Tetrahydroxybenzophenone*.—2 : 2′ : 4 : 4′-Tetrahydroxybenzophenone (0·4 g.) in a little alcohol and hydroxylamine hydrochloride (0·5 g.) in water (2 c.c.) and 10% sodium acetate solution (2 c.c.) were refluxed on a steam-bath for 1½ hr.; on cooling, 3 : 6-*dihydroxyxanthone oxime* separated. It crystallised from glacial acetic acid in plates, m. p. 283—285° (violet fluorescence in alkali) (Found : C, 63·8; H, 3·65; N, 6·1. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7; N, 5·8%).

3 : 6-*Dihydroxyxanthone*.—2 : 2′ : 4 : 4′-Tetrahydroxybenzophenone (0·5 g.) was heated in water (25 c.c.) at 200—220° (autoclave) for 2—2½ hr. On cooling, 3 : 6-dihydroxyxanthone was obtained in clusters of long needles. It was filtered off, washed, and crystallised from dilute pyridine. It did not melt below 330° and gave no ferric reaction. Its alkaline solution showed an intense violet fluorescence (Found : C, 68·6; H, 3·4. Calc. for $C_{13}H_8O_4$: C, 68·4; H, 3·5%) (Meyer and Conzetti, *Ber.*, 1897, **30**, 971, give decomp. >330°). It gave a diacetate (from alcohol), m. p. 205—206° (Kehrman, *Annalen*, 1910, **372**, 348, gives m. p. 204°), and a *dimethyl ether*, m. p. 186—187° (from alcohol) (Found : C, 70·0; H, 4·3. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

2 : 2′-*Dihydroxy*-4 : 4′-*dimethoxybenzophenone*.—2-Hydroxy-4-methoxybenzoic acid (0·9 g.), resorcinol monomethyl ether (1·0 g.), zinc chloride (3 g.), and phosphorus oxychloride (7 c.c.) were heated at 70—75° for 2 hr. The *benzophenone* crystallised from benzene in needles, m. p. 139—140° (0·4 g.) (Found : C, 65·4; H, 5·0. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%). It gave a brown ferric reaction, and was cyclised to 3 : 6-dimethoxyxanthone in water at 180—200°; this, when crystallised from alcohol, had m. p. and mixed m. p. 186—187°.

2 : 4 : 2′ : 3′ : 4′-*Pentahydroxybenzophenone*.—2 : 3 : 4-Trihydroxybenzoic acid (0·5 g.), resorcinol (0·5 g.), zinc chloride (3 g.), and phosphorus oxychloride (7 c.c.), heated at 70—80° for 1½ hr., gave the benzophenone, needles (from aqueous alcohol), (0·5 g.), m. p. 187—188°. It gave a dark brown ferric reaction and the alkaline solution became brown in air. Atkinson and Heilbron (*J.*, 1926, 2691) report m. p. 187°.

β-Resorcylic acid (1 g.), pyrogallol (1 g.), zinc chloride (6 g.), and phosphorus oxychloride (15 c.c.) when heated at 70—80° for 1 hr. yielded the same product, m. p. and mixed m. p. 187—188°.

3 : 4 : 6-*Trihydroxyxanthone*.—2 : 4 : 2′ : 3′ : 4′-Pentahydroxybenzophenone (0·5 g.) in water at 200—220° (2½ hr.) gave the xanthone, needles (from dilute alcohol), m. p. >340° (0·35 g.) (Dutta and Watson, *loc. cit.*, give m. p. >285°). This gave a dark green ferric colour and dissolved in alkali to an orange solution. Its triacetate (from acetic acid) had m. p. 209—210° and its *trimethyl ether* (from alcohol) melted at 153—154° (Found : C, 66·9; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9).

3 : 8-*Dihydroxyxanthone*.—γ-Resorcylic acid (0·5 g.), resorcinol (0·5 g.), zinc chloride (4 g.), and phosphorus oxychloride (7 c.c.) at 65—70° (1½ hr.) gave the xanthone which crystallised from dilute alcohol or dilute aqueous pyridine as needles, m. p. 246—247° (0·2 g.) (Graebe, *Annalen*, 1889, **254**, 302, gave m. p. 245—246°), giving a greyish-green ferric colour (Found : C, 68·3; H, 3·6. Calc. for $C_{13}H_8O_4$: C, 68·4; H, 3·5%). The diacetate formed needles, m. p. 155°, from dilute alcohol (Graebe, *loc. cit.*, gives m. p. 124—130°) (Found : C, 64·9; H, 3·6. Calc. for $C_{17}H_{12}O_6$: C, 65·4; H, 3·9%).

1 : 3 : 6-*Trihydroxyxanthone.*—A mixture of phloroglucinolcarboxylic acid (1 g.), resorcinol (1 g.), zinc chloride (6 g.), and phosphorus oxychloride (15 c.c.) was heated at 65—70° for 1½—2 hr. or kept at room temperature for 48 hr. The xanthone produced was very soluble in ethanol and crystallised from dilute alcohol. Sublimed in a high vacuum, it had m. p. 323—324° (decomp.) (Found : C, 64·0; H, 3·3. Calc. for $C_{13}H_8O_5$: C, 63·9; H, 3·3%). It gave a reddish-brown ferric colour. The triacetate, prepared by acetic anhydride and a few drops of pyridine at 130—140° for 2 hr., crystallised from alcohol in needles, m. p. 172—173° (Found : C, 61·4; H, 3·9. Calc. for $C_{19}H_{14}O_8$: C, 61·6; H, 3·8%), and the *trimethyl ether* from alcohol in needles, m. p. 155—156° (Found : C, 67·0; H, 4·8. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%).

β-Resorcylic acid (2·5 g.), phloroglucinol (2·5 g.), zinc chloride (10 g.), and phosphorus oxychloride (30 c.c.) at 65—70° (1½ hr.) yielded the same product, m. p. 323—324° (decomp.) (1·2 g.) (triacetate, m. p. and mixed m. p. 172—173°).

Lund, Robertson, and Whalley (*loc. cit.*) reported m. p. 332° (decomp.) (triacetate, m. p. 160°) and described it as almost insoluble in alcohol, acetone, benzene, dioxan, or ethyl acetate.

1 : 6-*Dihydroxy*-3-*methylxanthone.*—β-Resorcylic acid (1 g.), orcinol (1 g.), zinc chloride (3·5 g.), and phosphorus oxychloride (7 c.c.), heated at 70—75° for 2 hr., gave the *xanthone*, needles (from dilute pyridine), m. p. 326—327° (0·8 g.), which gave a dark green colour with ferric chloride and a greenish fluorescence in alcohol (Found : C, 69·4; H, 3·8. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%). Its *diacetate* crystallised from dilute acetic acid in needles, m. p. 161—162° (Found : C, 65·6; H, 4·3. $C_{18}H_{14}O_6$ requires C, 66·2; H, 4·3%).

1-*Hydroxy*-6-*methoxy*-3-*methylxanthone* was prepared by partially methylating the preceding xanthone with methyl sulphate (1·2 mol.), potassium carbonate, and acetone. When crystallised from alcohol, it had m. p. 155—156° and gave a green ferric reaction and a green fluorescence in alcohol (Found : C, 69·8; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

p-Orsellinic acid (0·5 g.), resorcinol (0·5 g.), zinc chloride (3 g.), and phosphorus oxychloride (7 c.c.) at 75—80° (1½ hr.) gave the same xanthone, m. p. and mixed m. p. 326—327°.

1 : 3-*Dihydroxy*-7-*methoxyxanthone* (iso*Gentisin*).—2-Hydroxy-5-methoxybenzoic acid (2 g.), phloroglucinol (2·2 g.), zinc chloride (6 g.), and phosphorus oxychloride (16 c.c.) were heated at 70—75° for 2 hr. The red solid obtained was sublimed at 230—240°/1—2 mm. and the yellow solid so obtained, when crystallised from dilute alcohol, had m. p. 239—240° (0·9 g.) (Shinoda, *J.*, 1927, 1984, gave m. p. 241° (Found : C, 65·0; H, 3·65. Calc. for $C_{14}H_{10}O_5$: C, 65·1; H, 3·9%). Acetylation yielded 1 : 3-diacetoxy-7-methoxyxanthone which, crystallised from acetic acid, had m. p. 210—212° (*idem, loc. cit.*, gives m. p. 211—212°). Methylation yielded 1 : 3 : 7-trimethoxyxanthone which crystallised from dilute methanol in plates, m. p. 171—173° (Rao and Seshadri, *loc. cit.*, give m. p. 171—173°). Demethylation of 1 : 3-dihydroxy-7-methoxyxanthone with hydriodic acid and acetic anhydride yielded 1 : 3 : 7-trihydroxyxanthone (gentisein) which crystallised from dilute alcohol in needles, m. p. 316—318° (olive-brown ferric colour) (*idem, ibid.*, give m. p. 316—318°).

1-*Hydroxy*-7-*methoxy*-3-*methylxanthone.*—2-Hydroxy-5-methoxybenzoic acid (2 g.), orcinol (2·2 g.), zinc chloride (6 g.), and phosphorus oxychloride (16 c.c.) at 70—75° (2 hr.) gave the *xanthone*, needles (from dilute pyridine), m. p. 155—156° (0·8 g.) (Found : C, 70·4; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%). The *acetate* crystallised from alcohol in needles, m. p. 157—158° (Found : C, 68·4; H, 4·7. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). Demethylation of 1-hydroxy-7-methoxy-3-methylxanthone (0·25) with hydriodic acid (10 c.c.; *d* 1·7) in acetic anhydride (5 c.c.) at 115—120° for 1½ hr. gave 1 : 7-dihydroxy-3-methylxanthone, m. p. 251—252° (from dilute pyridine), which gave a dark green ferric reaction (Kostanecki, *Ber.*, 1894, **27**, 1989, records m. p. 252°).

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